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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,529	11/28/2001	Kimberly A. Gillis	102729-14	3553

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,529	GILLIS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-35 have been cancelled and new claim 36 has been added.

The Examiner appreciates that Applicant points out the Examiner inadvertent typographic mistake concerning the pending of claims 1-7, 11-17. Thus claim 17 was properly not examined. The Examiner apologizes for any inconvenience due to the inadvertent typographic error.

Receipt of the petition filed on 07/19/04 is acknowledged. The petition has been considered. Upon reconsideration, the petition is moot for the following 2 reasons.

With regard to restriction requirement between Groups 1-20, the petition is moot because the restriction requirement between Groups 1-20 is withdrawn, upon reconsideration and in view of the current claim set. It is noted that claim 1 was a linking claim and should have been treated as such. Claim 1 has been cancelled and replaced with claim 36. Claim 36 is no longer a linking claim because no dependent claims directed to distinct inventions are present and linked by Claim 36. Should claims be filed which results in re-instatement of Claim 36 as a linking claim, the Examiner may follow the practice set forth in MPEP 809.

The request to withdraw the restriction requirement between Groups (1-20) and Groups (21-34) is moot in view of the cancellation of claims directed to Groups (21-34).

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION

Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

The omitted steps are: 1) Comparing the result of the test sample to that of the control sample, 2) Correlation between the results and the preamble.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

Claim 36 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention.

1. The limitation of "diagnosing development" of prostate cancer claimed in Claim 36 has no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for diagnosis of the presence or potential presence of prostate cancer in a subject (p.8, lines 10-11), or markers for risk of development of prostate cancer (p.9, line 1). There is however no mention of "diagnosing development" of prostate cancer.

The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

2. The limitation of "prognosis of progression" of prostate cancer claimed in Claim 36 has no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for monitoring progression of prostate cancer in a subject (p.5, lines 3-4), and prognosis of prostate disorders (p.3, line 9), identifying subjects at risk of development of prostate cancer (p.9, first line, and p.63, lines 17-19). There is however no mention of "prognosing development" of prostate cancer.

The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

A. Claim 36 is rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a method for detecting the presence of prostate cancer, comprising detecting an increase in the mRNA levels of the ID-1 of SEQ ID NO:4, and the ID-3 of SEQ ID NO:5, for reasons already of record in paper of 05/19/04.

Applicant submits a Declaration by Dr. Steven Haney, stating that 1) as described in the specification, ID-1 and ID-3 are found to be significantly differentially expressed between diseased and normal tissues, 2) ID-1 and ID-3 decrease in expression in prostate cancer cell line LNCaP after androgen treatment, and 3) those in the art, such as Horoszewicz et al, Thalmann et al, view LNCaP cells as in vitro model of prostate cancer, wherein LNCaP expresses prostatic acid phosphatase, androgen receptor, and PSA, which are hallmark of the prostatic phenotype.

Applicant asserts that well-characterized human cancer cell lines, such as LNCaP, are routinely used, and have proven to be highly predictive of in vivo results.

Applicant asserts that PSA was used as control, as was found to be increased as expected in prostate cancer cells.

The submission of the Declaration by Dr. Steven Haney, and the recitation of Horoszewicz et al, Thalmann et al is acknowledged and entered.

Applicant's arguments set forth in paper of 10/21/04 have been considered but are not deemed to be persuasive for the following reasons:

The specification discloses that a significant **difference** between the level of expression of the marker in the sample from the subject and normal level is an indication of prostate cancer (p. 4, lines 1-3). The specification further discloses that the levels of both ID-1 and ID-3 decrease in LNCaP cells treated with androgen, and that since current therapy for advanced prostate cancer is androgen ablation, this finding suggests that the level of ID-1 and ID-3 "will" increase in patients undergoing ablation therapy (p.84, lines 20-27).

It is noted however that it is not clear from the specification, and in the Declaration whether there is a difference in mRNA levels of ID-1 and ID-3 (SEQ ID NO:4 and 5) in primary prostate cancer tissue, as compared to normal control prostate tissue, nor is it clear that even if there is a difference, such difference is an increase or a decrease in mRNA levels of ID-1 and ID-3 (SEQ ID NO:4 and 5) in primary prostate cancer tissue, as compared to normal control, in view that the only data drawn to RNA difference are from prostate cancer cell culture studies, in which ID-1 and ID-3 mRNA expression decreases in androgen treated cells. It is not clear on what basis that the specification asserts that there is a differential expression of ID-1 and ID-3 mRNAs in

primary prostate cancer tissue as compared to normal tissues, in view of the teaching in the art that mutation or change in the level of expression of a gene is a chance event, Lewin, of record, and thus the level of expression of a gene in cancer is unpredictable. The teaching of Lewin is further confirmed in view that it is well known in the art that not every gene in a cancer cell is affected in carcinogenesis, such as mutation or changes in expression as compared to normal control cells. For example, Stanton, P et al, 1994, Br J Cancer, 70: 427-433 teach that the level of expression of epidermal growth factor receptor (EGFR) cannot be predicted from cell lines or tumors (p.432, second column, last paragraph), and that from ten tumors from which the cell lines are derived, only two of the tumors display elevated levels of EGFR, BICR6 and BICR18 proteins (table V on page 430, and first column, last paragraph of page 430) In other words, not only the level EGFR, BICR6 and BICR18 proteins are the same as normal control in 8 tumors, the rest of other proteins in table V are not different from normal control in all ten tumors. Similarly, Iehle, C et al, 1999, J Steroid Biochem Mol Biol, 68: 189-195, teach that although the level of 5-alpha-reductase-1 is increased in prostate cancer tissue, the level of the isoform 5-alpha-reductase-2 is the same as that of normal prostate (abstract). Abbaszadegan, M R, et al, 1994, Cancer Res, 54: 4676-4679, teach that the level of multidrug resistance-associated protein (MRP) detected in malignant hematopoietic cells is similar to the level found in normal hematopoietic cells (p.4678, second column, last 6 lines of second paragraph).

Thus without objective evidence, and in view that change in level of mRNA expression of a gene in a tumor as compared to normal corresponding cells is

unpredictable, one cannot predict that SEQ ID NO:4 and 5 would be differentially expressed in primary prostate cancer tissues versus corresponding normal cells, based solely on reduced mRNA expression in LNCaP cells treated with androgen.

Further, Applicant has not shown that ID-1 and ID-3 meet the criteria as tumor markers, as set out by Keesee et al, of record.

In addition, a decrease in both ID-1 and ID-3 mRNAs levels in LNCaP cells treated with androgen only indicates that ID-1 and ID-3 are sensitive to androgen treatment, and says nothing concerning diagnosis of prostate cancer, by detecting an increase in the mRNAs level of ID-1 and ID-3, because it is not clear what the levels of ID-1 and ID-3 mRNAs are in the normal prostate cell controls.

Concerning Applicant's arguments that well-characterized human cancer cell lines, such as LNCaP, are routinely used, and have proven to be highly predictive of in vivo results, the arguments are moot in view that there is no correlation between a decrease in both ID-1 and ID-3 mRNAs levels in LNCaP cells treated with androgen and an increase in ID-1 and ID-3 mRNA levels in primary prostate cancer cells as compared to normal prostate cancer cells as marker for diagnosis of prostate cancer, because it is not clear what the levels of ID-1 and ID-3 mRNAs are in the normal prostate cells as controls.

Moreover, even if Applicant shows that there is an increase in ID-1 and ID-3 mRNA levels in prostate cancer cells LNCaP as compared to normal prostate cancer cells, one cannot predict that the level of expression of genes in cells in culture, including LNCaP, would be predictive of in vivo conditions, due to cell culture artifacts.

Although LNCaP expresses prostatic acid phosphatase, androgen receptor, and PSA one cannot predict that other genes, including ID-1 and ID-3 would not be subjected to cell culture artifacts. Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line

assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

B. Claim 36 is also rejected under 112, first paragraph because claim 36 encompasses a method for detecting the presence of prostate cancer, comprising detecting an increase in the mRNA levels of the ID-1 of SEQ ID NO:4, "or" of the ID-3 of SEQ ID NO:5.

The above rejection to a method for detecting prostate cancer, comprising detecting an increase in the mRNA levels of SEQ ID NO:4 **and** 5, applies here as well, because one cannot predict that SEQ ID NO:4 **or** SEQ ID NO:5 alone increase in expression in prostate cancer, in view of lack of objective evidence and further in view of the teaching in the art, supra.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

C. Claim 36 is also rejected under 112, first paragraph because claim 36 encompasses a method for detecting the presence of prostate cancer, comprising detecting an increase in the "protein levels" of the ID-1 protein encoded by SEQ ID NO:4, and/or of the ID-3 protein encoded by SEQ ID NO:5.

Since one cannot predict that there is an increase in the mRNA level of expression of SEQ ID NO:4 and/or 5 in prostate cancer, in view of lack of objective evidence and further in view of the teaching in the art, supra, one cannot predict either that there is an increase in the protein levels of the ID-1 protein encoded by SEQ ID NO:4, and/or of the ID-3 protein encoded by SEQ ID NO:5.

Further, even if there is an increase in the mRNA level of expression of SEQ ID NO:4 and/or 5 in prostate cancer, one cannot extrapolate the mRNA level of expression of SEQ ID NO:4 and/or 5 to the protein level of the corresponding encoded protein.

One cannot predict that protein levels are correlated with steady-state mRNA levels or alterations in mRNA levels. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Further, Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Thus,

cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

D. Claim 36 is also rejected under 112, first paragraph because claim 36 encompasses a method for diagnosing development of or progression of prostate cancer, comprising detecting an increase in the expression of the ID-1 comprising SEQ ID NO:4, and/or of the ID-3 comprising SEQ ID NO:5.

Claim 36 encompasses a method for detecting development or progression of prostate cancer from preneoplastic conditions.

In view of lack of objective evidence and further in view of the teaching in the art, supra, one cannot predict either that there is an increase in the expression of the ID-1 comprising SEQ ID NO:4, and/or of the ID-3 comprising SEQ ID NO:5 during development of or progression of prostate cancer.

Further, even if there is an increase in the expression of SEQ ID NO:4 and/or 5 in prostate cancer, there is no correlation between increase in the expression of SEQ ID NO:4 and/or 5 in development or progression of prostate cancer from preneoplastic conditions, because there is no indication that SEQ ID NO:4 and/or 5 is responsible or involved in carcinogenesis of prostate cancer.

E. Claim 36 is also rejected under 112, first paragraph because claim 36 encompasses a method for detecting risk of development of or progression of

prostate cancer, comprising detecting an increase in the expression of the ID-1 comprising SEQ ID NO:4, and/or of the ID-3 comprising SEQ ID NO:5.

Since one cannot predict that there is an increase in the expression of SEQ ID NO:4 and/or 5 during development or progression of prostate cancer, in view of lack of objective evidence and further in view of the teaching in the art, supra, one cannot predict either that the expression of SEQ ID NO:4 and/or 5 in prostate cancer could be used for detecting risk of development of or progression of prostate cancer.

Further, even if there is an increase in the expression of SEQ ID NO:4 and/or 5 in prostate cancer, the specification provides neither guidance on nor exemplification of how to correlate the increase in the expression of SEQ ID NO:4 and/or 5 with the ability to use the increase in the expression of SEQ ID NO:4 and/or 5 for the assessment of risk of development of or progression of prostate cancer. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing an cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to the claimed invention. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches

that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In order to be useful several criteria should be taken into account including the association of ID-1 and/or ID3 with the pathway to prostate cancer, modification of ID-1 and/or ID3 from normal in patients at high risk for prostate cancer, shift of ID-1 and/or ID3 towards normal by intervention and finally, ID-1 and/or ID3 must be predictive of alteration in prostate cancer risk. As drawn to ID-1 and/or ID3 being predictive of development or progression of prostate cancer risk, it is not known at what stage of carcinogenesis or recurrent carcinogensis alteration of ID-1 and/or ID3, if any, are initiated or whether those alterations are mirrored in prostate cells. The specification does not present either guidance or exemplification that would enable one of skill in the art to determine the amount of increase that would be indicative of increased risk of development or progression of prostate cancer.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS
January 06, 2004